Asymmetric Hydrogenation of 1,4,5,6-Tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide Catalyzed by Trans-Chelating Chiral Diphosphine−Rhodium Complexes

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Highly enantioselective hydrogenation of 1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (**2**) was accomplished by a rhodium complex coordinated with a chiral diphosphine TRAP ligand, which is possible to chelate to a transition metal atom in a trans-manner. Of particular interest is that (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP gave 97% ee of the corresponding piperazine-2-carboxylic acid derivative (**3**) with (*S*) configuration, while the hydrogenation with (*R*,*R*)-(*S*,*S*)-MeTRAP−rhodium catalyst provided (*R*)-**3** with up to 85% ee. ^{31}P NMR studies of behavior of *i*-Bu- and MeTRAP−rhodium catalysts during the reaction suggest that the asymmetric hydrogenation of **2** with TRAPs may involve two competitive reaction pathways, giving their respective enantiomeric products **3**.

Introduction

Catalytic asymmetric hydrogenation of olefins using an optically active transition metal complex is one of the most progressing methodologies for preparation of a wide range of optically active compounds.[1] Especially, asymmetric hydrogenation of acyclic α-acetamidoacrylates has met with success, providing efficient preparation of optically active α-amino acids.[2,3] However, successful asymmetric hydrogenation of olefins has been still limited. Only a few examples of highly enantioselective hydrogenation of cyclic olefins have been reported.[4,5]

Optically active 2-substituted piperazines are important pharmacophores that can be found in many drugs. For example, (*S*)-4-(*tert*-butoxycarbonyl)piperazine-2-(*N*-*tert*-butyl)carboxamide (**1**) is an important synthetic intermediate of Merck HIV protease inhibitor Indinavir sulfate (Crixivan) (Figure 1).[6] The Merck research group has reported synthesis of optically active piperazine **1** by asymmetric hydrogenation of 1,4,5,6-tetrahydropyrazine-2-carboxamide **2** catalyzed by chiral rhodium complex,

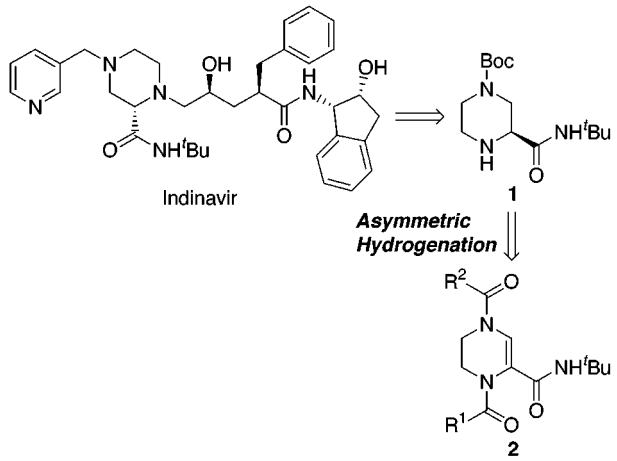

Figure 1.

in which high enantioselectivities have been, however, achieved under high hydrogen pressure (70−100 kg/cm^2)[7,8] or extremely low temperature (−40 °C).[9]

Previously, we have reported the preparation of trans-chelating chiral diphosphine TRAPs (Chart 1)[10,11] and

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(10) (*R*,*R*)-(*S*,*S*)-TRAP = (*S*,*S*)-2,2″-bis[(*R*)-1-(dialkylphosphino)ethyl]-1,1′-biferrocene.

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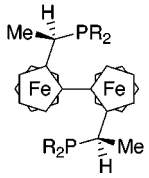
Chart 1



(*R*,*R*)-(*S*,*S*)-TRAP
R = Ph : PhTRAP
R = *i*-Pr : *i*-PrTRAP
R = *i*-Bu : *i*-BuTRAP
R = Bu : BuTRAP
R = Et : EtTRAP
R = Me : MeTRAP

their applications to some asymmetric reactions.[12−16] AlkylTRAP ligands bearing flexible linear alkyl groups on their phosphorus atoms were effective for the asymmetric hydrogenation of itaconates[17] and α-acetamidoacrylates including *β*,*β*-disubstituted ones.[18] In this paper, we report that a trans-chelating chiral diphosphine (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP is an effective chiral ligand for rhodium catalyzed asymmetric hydrogenation of **2**, which proceeds under mild condition to give (*S*)-piperazine-2-carboxamide **3** with up to 97% ee. Of particular interest is that its (*R*) enantiomer was prepared in high enantioselectivity by the rhodium-catalyzed hydrogenation with (*R*,*R*)-(*S*,*S*)-MeTRAP ligand, whose chiral sense is the same as that of (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP.[19]

Results and Discussion

Asymmetric Hydrogenation of 2a with Rhodium(I)−TRAP Complex. Asymmetric hydrogenations of 1-*tert*-butoxycarbonyl-4-phenoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (**2a**) were carried out in 1,2-dichloroethane (EDC, 0.25 M) at 50 °C under 1 kg/cm^2 of hydrogen for 24 h with 1 mol % of chiral catalyst prepared in situ from a variety of (*R*,*R*)-(*S*,*S*)-TRAP and [Rh(NBD)$_2$]PF$_6$ (eq 1). Enantiomeric excesses of **3a** thus obtained were determined by chiral HPLC analysis with SUMICHIRAL OA-2000. The results are summarized in Table 1. Phosphorus substituents of TRAP ligand remarkably affected not only enantioselectivity but also catalytic activity. Rhodium complex coordinated with Ph- and *i*-PrTRAP converted **2a** into **3a** in only 7 and 5% yields for 24 h, respectively (Table 1, entries 1 and 3). Bulky phenyl and isopropyl groups on phosphorus atoms of the chiral ligands might block coordination of **2a** to the rhodium metal center. Use of 2 mol % of PhTRAP−rhodium catalyst gave (*S*)-rich **3a** with 43% ee in 27% NMR yield (Table 1, entry 2). *i*-BuTRAP, bearing *β*-branched primary alkyl *P*-substituents, was the most effective chiral diphosphine for the asymmetric hydrogenation to give 97% ee of (*S*)-**3a** quantitatively (Table 1, entry 4). The *β*-branched alkyl group of *i*-BuTRAP may be important in achievement of the high enantioselectivity unlike Et- and BuTRAP bearing nonbranched alkyl *P*-substituents, which provided **3a** quantitatively but with low enantiomeric excess (Table 1, entries 5 and 6). To our surprise, MeTRAP−rhodium catalyst not only presented much lower catalytic activity but also showed a chiral sense of enantioselection opposite to that with other TRAP−rhodium catalyst employed, giving (*R*)-**3a** with 61% ee (Table 1, entry 7). The absolute configuration of **3a** was assigned by comparison of its retention time in the chiral HPLC analysis with that of the authentic sample prepared from (*S*)-piperazine-2-(*N*-*tert*-butyl)carboxamide.

THF and benzene can be used as solvent for the asymmetric hydrogenation without significant decrease

Table 1. Asymmetric Hydrogenetion of 2a Catalyzed by TRAP−Rhodium Complex[a]

entry	[Rh]	ligand[b]	solvent	convn, %[c]	ee (**3a**), %[d]	confign
1	[Rh(NBD)$_2$]PF$_6$	PhTRAP	EDC	7	*e*	
2[f]	[Rh(NBD)$_2$]PF$_6$	PhTRAP	EDC	27	43	*S*
3	[Rh(NBD)$_2$]PF$_6$	*i*-PrTRAP	EDC	5	*e*	
4	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	EDC	100	97	*S*
5	[Rh(NBD)$_2$]PF$_6$	BuTRAP	EDC	100	34	*S*
6	[Rh(NBD)$_2$]PF$_6$	EtTRAP	EDC	100	35	*S*
7	[Rh(NBD)$_2$]PF$_6$	MeTRAP	EDC	34	61	*R*
8	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	THF	100	95	*S*
9	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	C_6H_6	88	95	*S*
10	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	MeOH	0	*e*	
11	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	*i*-PrOH	23	85	*S*
12	[RhCl(COD)]$_2$	*i*-BuTRAP	EDC	0	*e*	
13[g]	[Rh(COD)$_2$]OTf	*i*-BuTRAP	EDC	3	*e*	
1[f]	[Rh(COD)$_2$]OTf	*i*-BuTRAP	EDC	53	93	*S*
15[g]	[Rh(COD)$_2$]ClO$_4$	*i*-BuTRAP	EDC	4	*e*	
16[f]	[Rh(COD)$_2$]ClO$_4$	*i*-BuTRAP	EDC	84	95	*S*
17[g]	[Rh(COD)$_2$]BF$_4$	*i*-BuTRAP	EDC	36	93	*S*
18[g]	[Rh(NBD)$_2$]PF$_6$	*i*-BuTRAP	EDC	75	95	*S*
19[g]	[Rh(NBD)$_2$]SbF$_6$	*i*-BuTRAP	EDC	85	96	*S*
20[g,h]	[Rh(NBD)$_2$]SbF$_6$	*i*-BuTRAP	EDC	100	96	*S*

[a] Reactions were carried out at 50 °C and 1 kg/cm^2 of hydrogen pressure for 24 h in 0.250 M solution of **2a** unless otherwise noted. The ratio of **2a**/[Rh]/ligand was 100:1:1.1. [b] (*R*,*R*)-(*S*,*S*)-TRAPs were used. [c] Determined by ^{1}H NMR analysis of evaporated reaction mixture. [d] Determined by chiral HPLC analysis with SUMICHIRAL OA-2000. [e] Not determined. [f] 2 mol % of catalyst was used. [g] Initial concentration of **2a** was 0.125 M. [h] The reaction was carried out at 2 kg/cm^2 of hydrogen pressure.

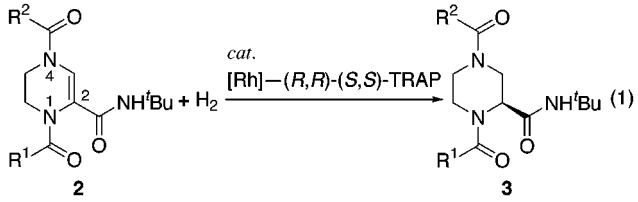


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Table 2. Asymmetric Hydrogenation of 2 Catalyzed by *i*-BuTRAP−Rhodium Complex[a]

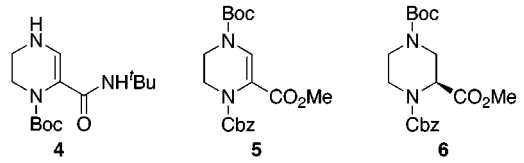
entry	R^1	R^2	substrate	convn, %[b]	product	ee, %[c]	confign
1	*t*-BuO	PhO	**2a**	85	**3a**	96	*S*
2	*t*-BuO	BnO	**2b**	76	**3b**	94	*S*
3	*t*-BuO	MeO	**2c**	89	**3c**	93	*S*
4	*t*-BuO	*t*-BuO	**2d**	8	**3d**		*S*
5[d]	*t*-BuO	*t*-BuO	**2d**	69	**3d**	87	*S*
6	BnO	PhO	**2e**	75	**3e**	96[e]	*S*
7	BnO	*t*-BuO	**2f**	40	**3f**	94	*S*
8	*t*-BuO	Me	**2g**	29	**3g**	55	*S*
9	Me	*t*-BuO	**2h**	18	**3h**	93[f]	*S*

[a] Reactions were carried out at 50 °C and 1 kg/cm^2 of hydrogen pressure for 24 h in 0.125 M solution of **2** unless otherwise noted. The ratio of **2**/[Rh(NBD)$_2$]SbF$_6$/(*R*,*R*)-(*S*,*S*)-*i*-BuTRAP was 100/1/1.1. [b] Determined by ^{1}H NMR analysis of evaporated reaction mixture. [c] Determined by chiral HPLC analysis with SUMICHIRAL OA-2000 unless otherwise noted. [d] The reaction was carried out with 2 mol % of catalyst in 0.25 M solution of **2d**. [e] Determined by chiral HPLC analysis with SUMICHIRAL OA-4100. [f] Determined by chial HPLC analysis with SUMICHIRAL OA-2200.

of the stereoselectivity (Table 1, entries 8 and 9), but 1,2-dichloroethane is superior in the solubilities of **2** and **3**. Alcoholic solvents, *i*-PrOH and MeOH, lowered catalytic efficiency (Table 1, entries 10 and 11). The neutral catalyst system generated from *i*-BuTRAP and [RhCl(COD)]$_2$ did not work as catalyst (Table 1, entry 12). Other *i*-BuTRAP−rhodium complexes generated from Rh(OBz)(COD), Rh(acac)(COD), Rh(acac)(CO)$_2$, and Rh(BPh$_4$)(COD) have no catalytic activity. Counteranion of cationic *i*-BuTRAP−rhodium complex affected the catalytic activity significantly (Table 1, entries 13−19). Rhodium complex bearing less coordinating counteranion, such as PF_6^- and SbF_6^-, revealed higher turnover frequency. However, the counteranions TfO^- and ClO_4^- caused remarkable decrease in the catalytic activity. Even weak interaction of such counteranions with the rhodium metal center might obstruct coordination of **2** on the catalyst, but the obstruction did not cause significant decrease in the enantioselectivity. Slightly higher hydrogen pressure (2.0 kg/cm^2) improved reaction rate without loss of enantioselectivity (Table 1, entry 20), but the hydrogenation at 100 kg/cm^2 yielded 20% ee of (*S*)-**3a** in only 8% conversion.

Effects of Protective Groups in 2. Prior to the asymmetric hydrogenation of 1,4,5,6-tetrahydropyrazine-2-carboxylic acid, the two enamino nitrogens and one carboxylic group of **2** were modified by common protective groups. The efficiency of the asymmetric hydrogenation of **2** was much dependent upon a choice of the protective groups. The enantioselective hydrogenation of various 1,4,5,6-tetrahydropyrazine-2-carboxamides **2a**−**h** with the 1- and 4-*N*-protective groups (0.125 M) was carried out at 50 °C under 1 kg/cm^2 of hydrogen gas in the presence of *i*-BuTRAP−rhodium complex, as summarized in Table 2. Substrate **2a**, which has the 1-*N*-*tert*-butoxycarbonyl and the 4-*N*-phenoxycarbonyl groups, presented the highest enantiomeric excess (96% ee) as well as a high chemical yield (85%) (Table 2, entry 1). The oxycarbonyl protective groups at the 1-nitrogen as well as the 4-nitrogen generally provided the satisfactory enantiomeric excesses. However, 1,4-bis(*tert*-butoxycarbonyl) derivative **2e** was reluctant to hydrogenation with *i*-BuTRAP−rhodium catalyst, probably due to its steric hindrance (Table 2, entry 4). Hydrogenations of **2g** and **2h**, which were both protected by acetyl group at either the 4- or 1-position, proceeded slowly to give the corresponding piperazine-2-carboxamide in 29 and 18% conversion after 24 h, but the enantioselectivities were significantly controlled by the position of *N*-acetyl group (**2g**, 55% ee; **2h**, 93% ee). This finding may indicate that the enantioselectivities of the asymmetric hydrogenation of **2** by means of *i*-BuTRAP ligand depend on the alkoxycarbonyl protective group on the 4-*N*-position rather than the 1-*N*-position. 1-*N*-*tert*-Butoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (**4**) (Chart 2) with no protection at the 4-*N*-position did not undergo the hydrogenation by *i*-BuTRAP−rhodium catalyst. The hydrogenation of methyl ester **5** proceeded up to 52% conversion (2 mol % catalyst, 24 h), giving **6** with 92% ee. Choice of protective groups for the 2-carboxylic functional group has some influence for the reactivities, but is not essential for high enantioselectivity.

Chart 2



4 **5** **6**

Table 3. Asymmetric Hydrogenation of 2 Catalyzed by MeTRAP−Rhodium Complex[a]

entry	R^1	R^2	substrate	convn, %[b]	product	ee, %[c]	confign
1	*t*-BuO	PhO	**2a**	32	**3a**	62	*R*
2	*t*-BuO	BnO	**2b**	21	**3b**	69	*R*
3	*t*-BuO	*t*-BuO	**2d**	21	**3d**	81	*R*
4	BnO	PhO	**2e**	31	**3e**	62	*R*
5	BnO	*t*-BuO	**2f**	60	**3f**	81	*R*
6[d]	BnO	*t*-BuO	**2f**	25	**3f**	81	*R*
7[e]	BnO	*t*-BuO	**2f**	85	**3f**	85	*R*
8	*t*-BuO	Me	**2g**	16	**3g**	51	*R*
9	Me	*t*-BuO	**2h**	16	**3h**	76	*R*

[a] Reactions were carried out at 50 °C and 1 kg/cm^2 of hydrogen pressure for 24 h in 0.250 M solution of **2** unless otherwise noted. The ratio of **2**/[Rh(NBD)$_2$]SbF$_6$/(*R*,*R*)-(*S*,*S*)-MeTRAP was 100/1/1.1. [b] Determined by ^{1}H NMR analysis of evaporated reaction mixture. [c] See Table 2. [d] [Rh(COD)$_2$]OTf was used. [e] The reaction was carried out at 2 kg/cm^2 of hydrogen pressure.

As previously mentioned, the asymmetric hydrogenations of **2** with MeTRAP−rhodium catalyst are noteworthy (Table 3). The enantioselectivities observed also depended upon the choice of the 4-*N*-protective group of **2** like those of the hydrogenation using *i*-BuTRAP. The *tert*-butoxycarbonyl group is the best protective group at the 4-*N*-position, giving 81% ee for the hydrogenation product at 50 °C and 1 kg/cm^2 of hydrogen pressure (Table 3, entries 3 and 5). Alkoxycarbonyl group at the 1-position hardly affected the stereoselectivity but controlled the reactivity. A highest enantioselectivity and a highest turnover number were attained in the asymmetric hydrogenation of **2d**, which has the 1-*N*-benzyloxycarbonyl and the 4-*N*-*tert*-butoxycarbonyl groups, forming (*R*)-**3d** with 85% ee in 87% conversion under 2 kg/cm^2 of hydrogen pressure for 24 h (Table 3, entry 7). In addition, the similar effect of the counteranion on catalytic activity, mentioned above, was also observed in the MeTRAP−rhodium-catalyzed asymmetric hydrogenation (Table 3, entry 6).

Mechanistic Studies. To shed light on the origin for the reverse enantioselection of MeTRAP to that of *i*-

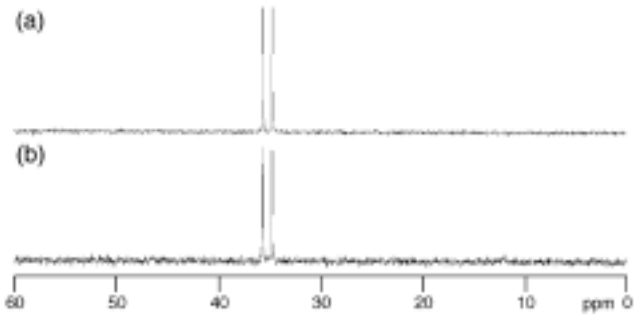


Figure 2. (a) ^{31}P NMR spectrum of the mixture of [Rh(NBD)$_2$]-SbF$_6$ and (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP after treatment with hydrogen. (b) ^{31}P NMR spectrum of the above sample after treatment with 5 molar equiv of **2c** under hydrogen atmosphere.

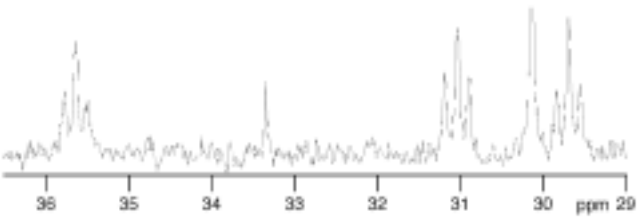


Figure 3. ^{13}C NMR spectrum of the mixture of [Rh(NBD)$_2$]-SbF$_6$ and (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP after treatment with hydrogen.

BuTRAP, behavior of *i*-BuTRAP− and MeTRAP−rhodium complexes during the asymmetric hydrogenation of **2c** was monitored by ^{31}P NMR measurement. Reaction of *i*-BuTRAP and [Rh(NBD)$_2$]SbF$_6$ in CD_2Cl_2 followed by treatment with hydrogen gave a single rhodium complex, *trans*-[Rh(*i*-BuTRAP)]SbF$_6$ (**7**), which showed a doublet peak at δ 35.17 ppm with 110 Hz of P−Rh spin coupling constant in the ^{31}P NMR spectrum (Figure 2a) and no signals at high magnetic field region (from −40 to 0 ppm) in the ^{1}H NMR spectrum. The trans-chelation of *i*-BuTRAP was also confirmed by the ^{13}C NMR spectra, where the resonances of the 13-carbons α to the phosphorus atoms are split into a virtually coupled triplet, indicating large virtual coupling constant by two phosphorus atoms coordinating to a rhodium atom (Figure 3).[20] No observable change of the ^{31}P NMR was detected after addition of 5 molar equiv of **2c** under hydrogen atmosphere (Figure 2b), while the substrate was converted to (*S*)-**3c** with 97% ee. The results may suggest that **7** is an active and the most thermodynamically stable catalyst prior to the rate-determining step of the catalytic hydrogenation. The complex **7** might undergo an oxidative addition with hydrogen, leading to an equilibrium with [RhH$_2$(*i*-BuTRAP)]$^+$ (**8**) which lies far to **7**. The existing **8** in low concentration might react with **2**,[21] which is hard to coordinate to the

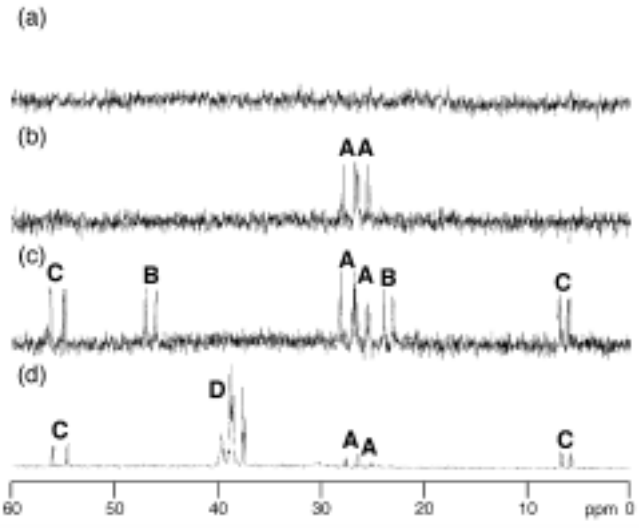


Figure 4. (a) ^{31}P NMR spectrum of the mixture of [Rh(NBD)$_2$]-SbF$_6$ and (*R*,*R*)-(*S*,*S*)-MeTRAP after treatment with hydrogen. (b) ^{31}P NMR spectrum of the above sample after treatment with 5 molar equiv of **2c**. (c) ^{31}P NMR spectrum of the mixture of [Rh(NBD)$_2$]SbF$_6$, (*R*,*R*)-(*S*,*S*)-MeTRAP and **2c** after treatment with hydrogen. (d) After 24 h.

i-BuTRAP−rhodium complex because of the steric repulsion between **2** and *P*-isobutyl groups of the catalyst.

On the other hand, similar experiment with MeTRAP is remarkably different from that of *i*-BuTRAP. Treatment of [Rh(NBD)$_2$]SbF$_6$ with MeTRAP under hydrogen atmosphere gave very broad signals in ^{31}P NMR in CD_2Cl_2 (Figure 4a). On addition of 5 equiv of **2c** into the CD_2Cl_2 solution, a pair of double doublet signals were observed at δ 25.67 (J_{P-Rh} = 132 Hz, J_{P-P} = 31 Hz) and 27.15 (J_{P-Rh} = 142 Hz, J_{P-P} = 31 Hz) (resonances **A**) (Figure 4b), which was identified as [Rh(**2c**)(MeTRAP)]$^+$ (**9**). The MeTRAP−rhodium catalyst may prefer coordination of **2** to oxidative addition of hydrogen. The small P−P spin coupling constant of **A** indicates that MeTRAP in the complex coordinates to a rhodium atom in cis-chelating manner. ^{31}P NMR spectrum of a mixture of [Rh-(NBD)$_2$]SbF$_6$, (*R*,*R*)-(*S*,*S*)-MeTRAP and **2c** (1:1:5) followed by treatment with hydrogen in CD_2Cl_2 for 10 min showed three sets of resonances corresponding to three cis-chelating MeTRAP−rhodium species including **9** (Figure 4c). The other two sets of double doublet resonances appear at δ 23.12 (J_{P-Rh} = 112 Hz, J_{P-P} = 27 Hz), 46.19 (J_{P-Rh} = 117 Hz, J_{P-P} = 27 Hz) (resonances **B**) and δ 6.10 (J_{P-Rh} = 106 Hz, J_{P-P} = 24 Hz), 55.28 (J_{P-Rh} = 167 Hz, J_{P-P} = 24 Hz) (resonances **C**). After 24 h, resonances **B** disappeared, and a small amount of **A** and **C** remained with new unidentified signal **D** which appears at 34−40 ppm resulting from decomposition of the catalyst (Figure 4d). The enantiomeric excess of **3c** isolated from the mixture was 61% ee (*R*). These results suggest that coordination of **2** would take precedence over oxidative addition of hydrogen in the hydrogenation using MeTRAP−rhodium complex.[22] The different mechanism and chelating mode from those with *i*-BuTRAP are operating for the reverse asymmetric induction in the hydrogena-

(20) Redfield, D. A.; Cary, L. W.; Nelson, J. H. *Inorg. Chem.* **1975**, *14*, 50−59.

(21) The mechanism involving an oxidative addition of hydrogen prior to olefin coordination is accepted for the hydrogenation of nonchelating olefins catalyzed by RhCl(PPh$_3$)$_3$, and causes deterioration of enantioselectivity in asymmetric hydrogenation of α-acetamidoacrylates: (a) Osborn, J. A.; Jardine, F. H.; Young J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711−1732. (b) Halpern, J. *Inorg. Chim. Acta* **1981**, *50*, 11−19 and references therein. (c) Daniel, C.; Koga, N.; Han, J.; Fu, X. Y.; Morokuma, K. *J. Am. Chem. Soc.* **1988**, *110*, 3773−3787. (d) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728−4739. (e) Sinou, D. *Tetrahedron Lett.* **1981**, *22*, 2987−2990.

(22) The precedence of olefin coordination to oxidative addition of hydrogen was observed in mechanistic studies of asymmetric hydrogenation of α-acetamidoacrylates: (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754 and references therein. (b) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 41−69.

tion of **2**. Low enantioselectivity of EtTRAP might arise from competition for the two mechanisms and the two chelation modes described above.

Conclusion

We found that trans-chelating chiral diphosphine TRAPs are effective chiral ligands for the asymmetric hydrogenation of **2** catalyzed by rhodium complex. The asymmetric hydrogenation proceeded smoothly under mild condition (50 °C, 1 kg/cm^2 of hydrogen pressure) to provide optically active 2-piperazinecarboxamide **3** with up to 97% ee. Of interest is that the two enantiomers of **3** were obtained with high enantiomeric excess by choice of *P*-substituents of (*R*,*R*)-(*S*,*S*)-TRAP ligand, i.e., tetrahydropyrazine **2f**, bearing 1-*N*-benzyloxycarbonyl and 4-*N*-*tert*-butoxycarbonyl groups, gave (*S*)- and (*R*)-**3f** with 94 and 85% ee by use of the chiral ligands (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP and (*R*,*R*)-(*S*,*S*)-MeTRAP, respectively. The reverse of enantioselectivity with the two TRAP ligands may be caused by the difference in their chelating mode on rhodium complex.

Experimental Section

General Methods. 1,2-Dichloroethane was distilled from CaH_2 under nitrogen, and 99.99999% of hydrogen was used. The (*R*,*R*)-(*S*,*S*)-TRAPs[11c] **2f**, **2h**, **4**, and **5**[7] were prepared according to literature procedures.

1-*tert*-Butoxycarbonyl-4-phenoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2a). To a solution of 1-*tert*-butoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butylcarboxamide) (**4**) (5.67 g, 20 mmol) and $NaHCO_3$ (1.92 g, 23 mmol) in EtOAc (40 mL) and MeCN (10 mL) was added phenyl chloroformate (3.30 g, 21 mmol) for 30 min at 50 °C. After 30 min of stirring at this temperature, the mixture was diluted with 10 mL of H_2O and extracted three times with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by a flash column chromatography on silica gel (hexane/EtOAc = 1/1) to give **2a** (6.37 g, 79%): white powder; mp 174 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.42 (s, 9H), 1.50 (s, 9H), 3.61−3.91 (m, 4H), 5.75 and 5.66 (a pair of br s, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.68 and 7.50 (a pair of s, 1H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 28.05, 28.82, 41.13 and 40.88 (a pair of s), 43.28 and 44.06 (a pair of s), 51.20, 82.70, 117.39, 120.17 and 119.57 (a pair of s), 121.42, 126.07, 129.53, 150.65, 151.08, 154.25, 163.31; IR (KBr) 3444, 1740, 1708, 1642 cm^{-1}. Anal. Calcd for $C_{21}H_{29}N_3O_5$: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.41; H, 7.20; N 10.41.

4-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2b): 92% yield; white powder; mp 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.39 (s, 9H), 1.47 (s, 9H), 3.52−3.61 (m, 2H), 3.61−3.70 (m, 2H), 5.22 (s, 2H), 5.72 and 5.66 (a pair of br s, 1H), 7.29−7.42 (m, 5H), 7.51 (s, 1H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 27.85, 28.64, 40.93 and 40.58 (a pair of s), 42.84 and 43.36 (a pair of s), 50.91, 68.43 and 68.20 (a pair of s), 82.38, 116.33, 120.58 and 119.82 (a pair of s), 128.26, 128.56, 128.62, 135.21, 152.41, 154.35, 163.37; IR (KBr) 3436, 1734, 1706, 1648 cm^{-1}. Anal. Calcd for $C_{22}H_{31}N_3O_5$: C, 63.29; H, 7.48; N, 10.06. Found: C, 63.21; H, 7.46; N 10.10.

1-*tert*-Butoxycarbonyl-4-methoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2c): 99% yield; white powder; mp 135 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.40 (s, 9H), 1.48 (s, 9H), 3.55−3.61 (m, 2H), 3.61−3.67 (m, 2H), 3.82 (s, 3H), 5.71 (br s, 1H), 7.47 (s, 1H); ^{13}C-{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 27.94, 28.73, 40.99 and 40.68 (a pair of s), 42.83 and 42.36 (a pair of s), 50.98, 53.52, 82.36, 116.35, 120.45 and 119.94 (a pair of s), 152.97, 154.25, 163.34; IR (KBr) 3332, 1738, 1705, 1654 cm^{-1}. Anal. Calcd for $C_{16}H_{27}N_3O_5$: C, 56.29; H, 7.97; N, 12.31. Found: C, 56.31; H, 7.86; N 12.06.

1-Benzyloxycarbonyl-4-phenoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2e): 95% yield; white powder; mp 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.24 (s, 9H), 3.68−3.93 (m, 4H), 5.20 (s, 2H), 5.66 (br s, 1H), 7.11−7.50 (m, 10 H), 7.68 (s, 1H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 28.39, 41.41, 43.20, 51.10, 68.35, 116.93, 120.51, 121.28, 126.03, 128.35, 128.47, 128.58, 129.46, 135.42, 150.56, 150.88, 154.92, 162.87; IR (KBr) 3320, 1739, 1714, 1638 cm^{-1}. Anal. Calcd for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.92; H, 6.24; N 9.63.

4-Acetyl-1-*tert*-butoxycarbonyl-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2g): 95% yield; white powder; mp 189 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.41 (s, 9H), 1.49 (s, 9H), 2.31 (s, 3H), 3.53−3.63 (m, 2H), 3.63−3.73 (m, 2H), 5.78 (br s, 1H), 7.31 (s, 1H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 21.32, 28.02, 28.79, 41.33, 51.21, 82.72, 116.78, 121.46, 154.29, 163.25, 168.75; IR (KBr) 3324, 1706, 1672, 1656 cm^{-1}. Anal. Calcd for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found: C, 59.32; H, 8.08; N 12.75.

1,4-Bis(*tert*-butoxycarbonyl)-1,4,5,6-tetrahydropyrazine-2-(*N*-*tert*-butyl)carboxamide (2d). The compound was prepared from **4** and $(Boc)_2O$ according to literature procedure for **2f** in 99% yield: white powder; mp 165 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.40 (s, 9H), 1.48 (s, 9H), 1.51 (s, 9H), 3.51−3.64 (m, 4H), 5.71 (br s, 1H), 7.47 (s, 1H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 28.06, 28.88, 41.24, 42.44, 51.00, 82.32, 82.70, 115.35, 121.79, 151.36, 154.58, 163.65; IR (KBr) 3340, 1718, 1646 cm^{-1}. Anal. Calcd for $C_{19}H_{33}N_3O_5$: C, 59.51; H, 8.67; N, 10.96. Found: C, 59.39; H, 8.53; N 10.90.

General Procedure of Asymmetric Hydrogenation of 2 Catalyzed by TRAP−Rhodium Complex. A solution of $[Rh(NBD)_2]SbF_6$ (1.3 mg, 2.5 μmol) and (*R*,*R*)-(*S*,*S*)-TRAP (2.8 μmol) in 1,2-dichloroethane (1.0 mL) was stirred at room temperature for 10 min under argon atmosphere, and **2** (0.25 mmol) was added. Immediately, the flask was cooled at −78 °C and repeatedly evacuated and filled with hydrogen. The reaction mixture was stirred at 50 °C for 24 h. After the solvent was evaporated, the residue was passed through a short silica gel column (hexane/EtOAc = 1/3) to give a mixture of **3** and unreacted **2** in quantitative yield.

1-*tert*-Butoxycarbonyl-4-phenoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3a): 100% yield; 97% ee (*S*); white powder; mp 183 °C; $[\alpha]^{20}_D$ −53.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.35 (s, 9H), 1.51 (s, 9H), 3.02−3.43 (br m, 3H), 3.84−4.10 (br m, 2H), 4.32−4.82 (br m, 2H), 5.93 (br s, 1H), 7.04−7.24 (m, 3H), 7.35 (t, J = 7.8 Hz, 2H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 28.23, 28.63, 40.82 (br s), 42.90, 43.25, 43.76, 51.30, 81.60, 121.92, 125.40, 129.27, 151.45, 154.09, 155.41, 168.23; IR (KBr) 3352, 1732, 1678 cm^{-1}. Anal. Calcd for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36. Found: C, 62.09; H, 7.76; N, 10.09.

4-Benzyloxycarbonyl-1-*tert*-butoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3b). The compound was obtained as a mixture with **2b** (**3b**/**2b** = 76/24): 94% ee (*S*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.31 (s, 9H), 1.48 (s, 9H), 2.98−3.30 (br m, 3H), 3.80−3.99 (br m, 2H), 4.34−4.65 (br m, 2H), 5.15 (s, 2H), 5.88 (br s, 1H), 7.28−7.43 (m, 5H).

1-*tert*-Butoxycarbonyl-4-methoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3c). The compound was obtained as a mixture with **2c** (**3c**/**2c** = 89/11): 93% ee (*S*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (s, 9H), 1.49 (s, 9H), 2.93−3.27 (br m, 3H), 3.77−4.01 (br m, 2H), 4.31−4.60 (br m, 2H), 5.91 (br s, 1H).

1,4-Bis(*tert*-butoxycarbonyl)piperazine-2-(*N*-*tert*-butyl)-carboxamide (3d). The compound was obtained as a mixture with **2d** (**3d**/**2d** = 69/31): 87% ee (*S*); ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.33 (s, 9H), 1.46 (s, 9H), 1.48 (s, 9H), 2.92−3.22 (br m, 3H), 3.72−3.94 (br m, 2H), 4.29−4.56 (br m, 2H), 5.83 (br s, 1H).

1-Benzyloxycarbonyl-4-phenoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3e). The compound was obtained as a mixture with **2e** (**3e**/**2e** = 75/25): 96% ee (*S*); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (s, 9H), 3.00−3.52 (br

m, 3H), 3.92−4.21 (br m, 2H), 4.36−4.87 (br m, 2H), 5.09−5.33 (br AB q, 2H), 5.80 (br s, 1H), 7.02−7.55 (m, 10H).

1-Benzyloxycarbonyl-4-*tert*-butoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3f). The compound was obtained as a mixture with **2f** (**3f**/**2f** = 40/60): 94% ee (*S*); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (s, 9H), 1.46 (s, 9H), 2.83−3.30 (br m, 2H), 3.13 (dd, J = 4.5, 13.8 Hz, 1H), 3.72−4.08 (br m, 2H), 4.35−4.70 (br m, 2H), 5.15 (d, J = 12 Hz, 1H), 5.21 (d, J = 12 Hz, 1H), 5.69 and 5.97 (a pair of br s, 1H), 7.28−7.41 (m, 5H).

4-Acetyl-1-*tert*-butoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3g). The compound was obtained as a mixture with **2g** (**3g**/**2g** = 29/71): 55% ee (*S*).

1-Acetyl-4-*tert*-butoxycarbonylpiperazine-2-(*N*-*tert*-butyl)carboxamide (3h). The compound was obtained as a mixture with **2h** (**3h**/**2h** = 18/82): 93% ee (*S*).

Asymmetric Hydrogenation of 2f using (*R*,*R*)-(*S*,*S*)-MeTRAP−Rhodium Catalyst. A solution of $[Rh(NBD)_2]SbF_6$ (1.3 mg, 2.5 μmol) and (*R*,*R*)-(*S*,*S*)-MeTRAP (1.5 mg, 2.7 μmol) in 1,2-dichloroethane (1.0 mL) was stirred at room temperature for 10 min under argon atmosphere. The solution was transferred by a cannula to an argon-filled glass autoclave, in which **2f** (105 mg, 0.25 mmol) was placed beforehand. Immediately, the autoclave was cooled to −78 °C and repeatedly evacuated and filled with hydrogen. Hydrogen was introduced into the vessel until the pressure gauge indicated 1 kg/cm^2. The reaction mixture was stirred at 50 °C for 24 h. After the solvent was evaporated, the residue was passed through a short silica gel column (hexane/EtOAc = 1/3) to give a mixture of 85% ee of (*R*)-**3f** and **2f** quantitatively. The mixture was purified by recrystallization from hexane/EtOAc to give 100% ee of (*R*)-**3f** (17.1 mg, 16%): Colorless crystal; mp 135 °C; $[\alpha]^{20}_D$ +32.9 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.29 (s, 9H), 1.46 (s, 9H), 2.83−3.30 (br m, 2H), 3.13 (dd, J = 4.5, 13.8 Hz, 1H), 3.72−4.08 (br m, 2H), 4.35−4.70 (br m, 2H), 5.15 (d, J = 12.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.69 and 5.97 (a pair of br s, 1H), 7.28−7.41 (m, 5H); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$) δ 28.23, 28.50, 41.16 (br s), 41.96 (br s), 43.02 (br s), 51.44, 55.71 (br s), 67.78, 80.41, 128.07, 128.30, 128.63, 136.22, 154.63, 156.08, 167.69; IR (KBr) 3360, 1704, 1696, 1678 cm^{-1}. Anal. Calcd for $C_{22}H_{33}N_3O_5$: C, 62.99; H, 7.93; N, 10.02. Found: C, 62.78; H, 7.87; N, 10.00.

NMR Study for the Reaction of *i*-BuTRAP and $[Rh(NBD)_2]SbF_6$ under Hydrogen Atmosphere. A mixture of $[Rh(NBD)_2]SbF_6$ (5.2 mg, 10 μmol) and (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP (7.1 mg, 10 μmol) in CD_2Cl_2 (0.7 mL) was stirred at room temperature for 5 min under argon atmosphere. The solution was degassed by three freeze−pump−thaw cycles, before hydrogen was introduced into the reaction vessel. The mixture was stirred for 10 min and transferred into a hydrogen-filled NMR tube via a cannula. The NMR spectra are as follows: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.71 (d, J = 6.3 Hz, 6H), 0.85−0.91 (m, 18H), 1.07−1.18 (m, 6H of norbornane × 2), 1.36−1.68 (m, 12H and 4H of norbornane × 2), 1.63 (dt, J^3_{H-H} = 7.2 Hz, $|J^3_{H-P} + J^5_{H-P'}|$ = 11.0 Hz, 6H), 2.13−2.19 (m, 2H of norbornane × 2), 3.13 (tq, $|J^2_{H-P} + J^4_{H-P'}|$ = 6.6 Hz, J^3_{H-H} = 7.2 Hz, 2H), 4.19−4.24 (m, 2H), 4.36 (s, 10H), 4.51 (t, J = 2.6 Hz, 2H), 4.57 (dd, J = 1.4, 2.6 Hz, 2H); ^{13}C {^{1}H} NMR (75.5 Hz, CD_2Cl_2) δ 16.05, 24.15, 24.71, 24.92 (2C), 26.54, 26.67, 29.69 (t, $|J^1_{C-P} + J^3_{C-P}|$ = 21 Hz), 30.15 (norbornane), 31.04 (t, $|J^1_{C-P} + J^3_{C-P}|$ = 23 Hz), 35.63 (t, $|J^1_{C-P} + J^3_{C-P}|$ = 21 Hz), 36.97 (norbornane), 38.80 (norbornane), 66.07, 68.62, 71.11, 71.80, 82.40, 92.35; ^{31}P {^{1}H} NMR (121.5 MHz, CD_2Cl_2, 85% H_3PO_4) δ 35.17 (d, J_{P-Rh} = 110 Hz).

No observable change in the ^{31}P NMR spectrum was detected after addition of **2c** (17.5 mg, 54 μmol) in CD_2Cl_2 (0.2 mL) into the NMR sample.

^{31}P NMR Study of Behavior of *i*-BuTRAP−Rh Complex during Asymmetric Hydrogenation of 2c. A mixture of $[Rh(NBD)_2]SbF_6$ (5.3 mg, 10 μmol) and (*R*,*R*)-(*S*,*S*)-*i*-BuTRAP (7.1 mg, 11 μmol) in CD_2Cl_2 (0.7 mL) was stirred at room temperature for 5 min under argon atmosphere. After **2c** (17.5 mg, 54 μmol) was added, the solution was degassed by three freeze−pump−thaw cycles, before hydrogen was introduced into the reaction vessel. The mixture was stirred for 10 min and transferred into a hydrogen-filled NMR tube via a cannula. Hydrogenation of **2c** proceeded slowly (completed within 7 h) to give (*S*)-**3c** in 97% ee, but the sample gave the same ^{31}P NMR spectrum as $[Rh(i\text{-BuTRAP})]SbF_6$ during the reaction: ^{31}P {^{1}H} NMR (121.5 MHz, CD_2Cl_2, 85% H_3PO_4) δ 35.17 (d, J_{P-Rh} = 110 Hz).

^{31}P NMR Study for Reaction of MeTRAP and $[Rh(NBD)_2]SbF_6$ under Hydrogen Atmosphere. The experiment was performed according to the procedure described above. Only very broad peaks were observed in ^{31}P NMR measurement. After **2c** (6.8 mg, 20 μmol) in CD_2Cl_2 (0.2 mL) was added to the solution in CD_2Cl_2, a pair of double doublet peaks appeared in the ^{31}P NMR spectrum: ^{31}P {^{1}H} NMR (121.5 MHz, CD_2Cl_2, 85% H_3PO_4) δ 25.67 (dd, J_{P-P} = 31 Hz, J_{P-Rh} = 132 Hz), 27.15 (dd, J_{P-P} = 31 Hz, J_{P-Rh} = 142 Hz).

^{31}P NMR Study of Behavior of MeTRAP−Rh Complex during Asymmetric Hydrogenation of 2c. The experiment was performed according to the procedure described above. Three sets of double doublet signals appeared in ^{31}P NMR spectrum as shown in Figure 4c. After 24 h, 50% of **2c** was converted into (*R*)-**3c** (61% ee).

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